



Case Report

A Rare and Novel Pathogenic Variant of the PINK1 Gene Associated with Early-onset of Parkinson's Disease - A Case Study

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ABSTRACT

We reported a case of rare and novel PINK 1 gene variant associated with Early-onset Parkinson's Disease (EOPD) in 40-year-old male patient. Patient was presented with clinical indications of dystonia (left>right), hemidystonia and dystonic tremors. Patient has family history (elder sister) of parkinsonism diagnosed with PD at the age of 38 years, and the condition slowly deteriorated and died. Patient was subjected to MRI investigations of brain two years before on clinical condition of right upper limb involuntary movement since from past one year. MRI findings revealed few small non-specific foci of T2 hyperintensity seen scattered in the bilateral frontal white matter (R>L) incidental findings of doubtful significance. Patient was referred for whole exome sequencing. The exome data analysis identified a "homozygous autosomal recessive variant" of PINK1 gene with variant nomenclature "c.823_825delATC; p.Ile275del (Chr1:20644531 ACAT>A)" could be associated with EOPD with characterized rare clinical phenotypic manifestations in the form of hemidystonia.

Keywords: Parkinson's disease; PINK1 gene; Autosomal recessive; Homozygous; Dystonia

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with symptoms that are being developed slowly over the years, including motor symptoms *viz.* bradykinesia, rigidity, tremor, and postural instability as well as non-motor symptoms like cognitive changes, hallucination and delusion, depression, sleep disorders, behavioural changes, constipation, and sensory abnormalities [1]. Parkinson disease is more common in men (1.4:1.0 male-to-female ratio). Most cases of PD are idiopathic, but there are known genetic and environmental contributions [2].

In a review of literature study carried out by Selvaraj and Piramanayagam reported that mutations on some

genes *viz.* SNCA, UCHL1, GIGYF2, GBA, LRRK2, PRKN, PINK1, ATP13A2, PLA2G6, and FBXO7 could be the cause of PD. Among these, Parkin RBR E3 Ubiquitin Protein Ligase (PRKN) and PTEN Induced Kinase 1 (PINK1) genes, both involved in a metabolic pathway are known to be associated with Early-onset Parkinson's disease (EOPD) [3]. PRKN is described as the most common cause of autosomal recessive PD accounting for about 49% of familial EOPD, and 20% of sporadic EOPD [1].

Herein we aimed to present a case of rare and novel pathogenic variant of the PINK1 gene associated with EOPD.

Case Presentation

A 40-year-old male patient presented on June, 2023 with a history of postural abnormality *viz.* bending of body towards left side and elevation of the right shoulder (Figure 1) since from past 2 years and it was progressive slowly. The detailed neurological examinations of the patient were as follows; Highest Mental Function (HMF) with Mini-Mental State Examination (MMSE) score 30, cranial nerves and speech was normal. Normal eye movement with normal saccadic and pursuit movements. No dysarthria or dysphagia. Motor examination revealed normal power of 5/5, deep tendon reflexes were elicitable (2+), plantar flexors and normal sensory examination. Patient

movement phenomenon observed in the clinic was suggestive of left hemidystonia with tilting of trunk towards left side and intermittent elevation of right shoulder. Gait examination revealed dystonic posturing towards left side of the body with lurching gait. Patient was unresponsive to antiparkinsonian disease medication (trial of levodopa and carbidopa). Patient has family history (elder sister) of parkinsonism, diagnosed at the age of 38 years and treated with levodopa and carbidopa by different neurologists in another hospital. However, condition slowly deteriorated and died.



Figure 1: Showing postural abnormality of patient (i.e., bending of body towards left side and elevation of the right shoulder).

Two years before i.e., in June, 2021 patient was subjected to magnetic resonance imaging (MRI) investigations of brain on clinical condition of right upper limb involuntary movement since in the past one year. Brain MRI findings revealed few small non-specific foci of T2 hyperintensity seen scattered in the bilateral frontal white matter (R>L) incidental findings of doubtful significance.

Patient was referred for whole exome sequencing on June 2023. The total genomic DNA was extracted from the biological sample using column-based method and DNA quality and quantity were assessed using electrophoretic and Qubit method. The quality control qualified genomic DNA was randomly fragmented and ligating sequencing adapters were added to both ends of

DNA fragments. Sequencing libraries were size-selected using beads to optimal template size and amplified by polymerase chain reaction. The regions of interest (exons and flanking intronic targets) are targeted by hybridization-based target capture method. Sequencing libraries that passed the quality control were sequenced on Ultra-high-depth Whole Genome Sequencing instrument (Model: DNBSEQ-T10x4RS; Make: MGI) using paired-end chemistry. Reads were assembled and are aligned to reference sequences based on National Center for Biotechnology Information (NCBI) Ref Seq transcripts and human genome build GRCh38. Data was filtered and analyzed to identify variants of interest related to patients' clinical phenotype.

The exome data analysis identified a homozygous non-frameshift deletion “c.823_825delATC; p.Ile275del

(Chr1:20644531 ACAT>A)” in PINK1 gene as represented in Table 1.

Table 1: Variants in PINK1 gene.

Gene and Transcript	Exon	Variant Nomenclature	Zygoty	Disease	Inheritance
PINK1 NM_032409.3	4	c.823_825delATC p.Ile275del Chr1:20644531 ACAT>A	Homozygous	Early onset Parkinson disease-6 (OMIM#605909)	Autosomal recessive

Discussion

The PINK1 gene carries the instructions that cells need to make a mitochondrial protein called PTEN induced putative kinase 1. This protein helps protect mitochondria from damage and helps keep that damage from replicating when cells reproduce. Mutations to the PINK1 gene could result in a loss of this protection. Also, PINK1 gene works together with another gene called PARKIN to keep the mitochondrial neurons working correctly. PINK1 and PARKIN appear to act as quality control. They send signals that enable cells to destroy damaged mitochondria. When this doesn't happen, damaged mitochondria can reproduce, and unhealthy cell function can continue to occur. As a result, mitochondria in these regions don't produce energy correctly. This is known to lead to PD and other brain function conditions. People who inherit this PINK1 gene mutation are more likely to develop PD before age 45 than people without genetic forms of PD [4].

Rogaeva et al. identified disease-causing PINK1 mutations in 2 of 289 unrelated North American patients with early- or late-onset PD, suggesting that mutations in this gene are a rare cause of EOPD [5]. Ton et al. reported homozygous mutant genotype p.340T of the PINK1 gene and the frequency of this variant is higher in EOPD cohort when compared with control group ($p = 0.0001$, $OR = 5.704$) indicating this variant might be a risk factor for EOPD [1]. Valente et al. mapped a locus for a rare familial form of PD to chromosome 1p36 (PARK6) and further shown that mutations in PINK1 are associated with PARK6 resulting in increased susceptibility to cellular stress. It was well

known that PINK 1 gene is mitochondrial origin and exert protective effect on the cell that is abrogated by the mutations in PINK1 gene suggesting molecular link between mitochondria and the pathogenesis of PD [6]. The fundamental mechanism underlying PINK 1 gene mutation and pathogenesis of PD was explained by Morais et al. that PINK1 deficiency or clinical mutations impact on the function of Complex I of the mitochondrial respiratory chain resulting in mitochondrial depolarization and increased sensitivity to apoptotic stress in mammalian cells and tissues. The clinical relevance of PINK 1 gene mutation and pathogenesis of PD was further demonstrated by the fact that human wild type PINK1 gene can rescue Complex I deficiency, but not PINK1 gene containing clinical mutations [7].

Dystonia is an unusual presentation in sporadic and familial PD [8]. Dystonia is often a presenting sign in EOPD. Classically, this manifests as action dystonia in a distal leg, occasionally only precipitated by exercise [9]. Over 30% of individuals with recessive mutations in PARK2, which encodes parkin, present with leg dystonia. Distal leg dystonia is also a common presentation of recessive mutations in PARK6 (PINK1) and PARK7 (DJ1) mutations [10]. In concurrence with these literature findings, in our case study patient was presented with left hemidystonia with intermittent elevation of right shoulder since from past two years duration without any evidence of parkinsonism. Though his elder sister presented as parkinsonism and treated in another hospital by a different neurologist, surprisingly her younger brother presented with hemidystonia without any evidence of parkinsonism. Hence, different

phenotypic presentation of same gene in the same family.

Conclusion

In conclusion, the homozygous autosomal recessive variant of PINK1 gene with variant nomenclature c.823_825delATC; p.Ile275del (Chr1:20644531 ACAT>A) identified in this case as hemidystonia, phenotypic variant of PINK1 gene, while elder sister being affected with parkinsonism in the same family.

Patient Consent Declaration

Authors hereby declare that they have obtained patient consent.

Conflict of Interest

None.

Funding

None to declare.

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